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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,522	12/01/2000	Hiroshi Nagai	1830/49264	8049

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/647,522	Applicant(s) NAGAI ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19-21,23-31 and 33-35* is/are pending in the application.

4a) Of the above claim(s) *19-21,23-31 and 33-35* is/are withdrawn from consideration.

5)☒ Claim(s) *17* is/are allowed.

6)☒ Claim(s) *22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

The Amendment and Response filed October 15, 2002 (Paper No. 9)has been entered and considered. Claims 18, 32, and 36 have been cancelled. Therefore, Claims 17, 19-21, 23-31, 33-35 are pending. Claims 19-21, 23-31, and 33-35 are withdrawn from consideration as being drawn to a non-elected invention for the reasons explained below. Claims 17 and 22 have been considered in this Office Action.

Rejections Withdrawn

The rejection of Claims 17 under 35 U.S.C. 102(b) as being anticipated by Allison et al. (Infect. Immun. (1997) p. 2765-2771; cited in Paper No. 6) is withdrawn in light of the cancellation of Claims 18, 32, and 36 and the amendment of Claim 17.

The rejection of Claims 17, 18, 32, and 36 under 35 U.S.C. 102(b) as being anticipated by Sato (Ochanomizu Igaku Zasshi (1985) 33(2) 131-151 (abstract) Toxcenter [Bioscience on STN] Retrieved from: STN International, Columbus, OH, USA. Accession Number CA10321175714H) is withdrawn in light of the cancellation of Claims 18, 32, and 36 and amendment of Claim 17.

The rejection of Claims 17, 18, 32, and 36 under 35 U.S.C. 102(b) as being anticipated by Tamkun et al. (Biochim. Biophys Acta (1981) 667: 87-98) is withdrawn in light of the cancellation of Claims 18, 32, and 36 and the amendment of Claim 17.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated protein comprising the amino acid sequence of SEQ ID NO:5 wherein said protein has hemolytic activity, does not reasonably provide enablement for a protein containing at least one cysteine residue in the molecule, wherein the protein is produced by expression of a polynucleotide obtainable through isolation from a *Carybdea rastonii* gene library by hybridization with a synthesized polynucleotide based on an amino acid sequence selected from the group consisting of SEQ ID NO:1-3 or 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, practicing the claimed invention commensurate in scope with the claims would require undue experimentation. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the Claims

Claim 22 encompasses any protein having any activity that is produced by expression of a polynucleotide sequence encoding SEQ ID NO:1-3 or 5 or a polynucleotide which hybridizes to the polynucleotide encoding SEQ ID NOs: 1-3 or 5. Given the appropriate conditions, hybridization can occur between completely unrelated polynucleotide sequences. Therefore, this claim encompasses proteins having an infinite number of sequences and functions.

Amount of Direction or guidance presented/ presence or absence of working examples

The present Specification describes and provides working examples of the isolation, sequencing, and determination of function of a full-length protein of SEQ ID NO:5 isolated from C. rastonii. The function of the short peptides (14-16 amino acids in length) of SEQ ID NOs: 1-3 is not disclosed and the Specification does not indicate that these short peptides maintain the hemolytic activity of the full-length protein. After the protein of the invention was isolated, the sequences of these peptides (SEQ ID NOs: 1-3) appear to have been used as tools to obtain the sequence of the full length cDNA encoding the protein of the invention and the specification does not provide any further guidance or examples as to the functions of the individual peptides. The present Specification does not provide any guidance or examples of using the claimed proteins as a pharmaceutical or as a pesticide. The present Specification does not teach how the claimed proteins function in hemolysis (e.g. catalytic function or binding function) and does not even teach whether or not the hemolytic activity observed correlates with the toxicity of jellyfish stings. While there is no requirement that the Specification teach

the biochemical function that results in hemolysis, in the present case, such information would be essential to understanding whether or not the hemolytic activity causes the toxicity of the jelly fish sting rather than another activity the protein may have.

Nature of the Invention

The invention involves the discovery of a single protein (SEQ ID NO:5) isolated from *C. rastonii* that appears to have hemolytic activity. The Specification asserts that the proteins described therein can be used to develop medicine for treating jellyfish stings, or as a drug with platelet agglutination effect or as a pesticide. However, the Specification does not teach how the proteins would be used in these methods. The nature of the claimed invention involves prediction of protein function from a single unique amino acid sequence with unknown biochemical activity, the use of this protein and unknown related proteins in the treatments and pesticides.

Predictability/Unpredictability

Merely predicting protein function from amino acid sequence information is considered highly unpredictable as evidenced by Smith et al. (Nature Biotechnol. (1997) 15: 1222-1223), Doerks et al. (Trends in Genetics (1998) 14(6) : 248-250), and Zhang et al. (Proc. Natl. Acad. Sci. (2000) 97(6): 2550-2555). In fact, Smith et al. Doerks et al. discuss the difficulties and common errors in attempting to predict the function of a given protein based on its amino acid sequence similarity to other proteins of known function. The present case would be even more difficult than those discussed in Smith et al. and Doerks et al. because the sequence of the protein of the present invention does not appear to be closely related to any other known protein. Moreover, the

Specification does not provide guidance as to the biochemical function that results in hemolysis. Therefore, one of skill in the art would not have any basis to predict what affect changing any particular amino acid residue would have on protein function. Moreover, since function is requires a particular protein structure and since protein structure depends on amino acid residues throughout the protein sequence (e.g. a protein fold may involve contacting two cysteines on either end of the protein sequence), one of skill in the art would not expect that a short peptide of 14-16 amino acids would maintain the function of the corresponding full length, 450 amino acid, protein. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions. The instant claims encompass proteins with any number of amino acid substitutions, deletions, or additions. However, Applicant has provided no guidance beyond the mere disclosure of a single, naturally occurring protein to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions, additions or deletions), and the nature and extent of changes that can be made in these positions. While one of skill in the art may know how to screen proteins for hemolytic activity, this

is not adequate guidance as to the nature of the proteins that may be constructed, but is merely an invitation to the artisan to use the disclosed protein as a starting point for further experimentation.

State of the Prior Art and Relative Skill in the Art

A thorough search of the prior art indicates that at the time of the invention, a protein with sequence similar to that of SEQ ID NO:5 was unknown. There were no known pharmaceuticals containing a related protein from the toxins of jellyfish that were used to treat jellyfish stings. In fact, Nagai et al. state that the mode of action of jelly fish toxins is not understood and that a better understanding of that mode of action is necessary to permit the development of treatments for jelly fish stings (see Nagai et al. (Biochem. Biophys. Res. Comm. (2000) 275: 582-588). Thus, it appears that further characterization of the protein was required before those of skill in the art would be able to use the protein in any methods of treatment.

At the time of the invention, there were no known pesticides made from proteins related to the claimed proteins or from other jellyfish toxins. The Specification does not provide guidance as specifically how it would be used and what it would be used for (e.g. killing weeds, insects, funguses, or viruses, etc.?). Thus, it appears that further characterization of the protein would be required before those of skill in the art would be able to use the protein of the invention as a pesticide.

And, as explained above, at the time of the invention, one of skill in the art considered protein function prediction based on amino acid sequence alone highly unpredictable.

Quantity of Experimentation

For the reasons stated above, a large quantity of experimentation would be necessary to generate the infinite number of modified proteins recited in the claims and possibly screen same for hemolytic activity. Moreover, undue experimentation would be required to characterize the peptides of SEQ ID NOs: 1-3 so as to determine their function. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the disclosed protein that are required for the functional and structural integrity of the protein. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Response to Arguments: Applicant argument that one of skill in the art could make the claimed invention because the claimed proteins are produced by a polynucleotide that is obtainable by hybridizing a polynucleotide according to SEQ ID NOs: 1-3 or 5 with materials from a C. rastonii gene library has been considered but is not deemed persuasive for the reasons described above and as follows. Such guidance is not adequate as to the nature of the proteins that may be constructed, but is merely an invitation to the artisan to use the disclosed protein as a starting point for further experimentation and a wish to know those protein sequences that have

hemolytic function. As explained above, to practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the disclosed protein that are required for the functional and structural integrity of the protein. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce and use a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation. Thus, the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Applicant is referred to the Written Description Guidelines published January 5, 2001 in the Federal Register, Vol. 66, No. 4, p. 1099-1111 (also available at www.uspto.gov).

Rejection: The specification does not set forth the invention in terms of distinguishing, identifying characteristics sufficiently detailed to show that applicant was

in possession of the claimed invention. The specification does not show 1) what distinguishing, identifying characteristics of the amino acid sequence of SEQ ID NO: 5 provides hemolytic activity, 2) what distinguishes a protein with hemolytic activity isolated from the nemocyst of Carybdea rastonii from hemolytic proteins isolated from other sources, or 3) any distinguishing, identifying characteristics of a protein expressed from a polynucleotide sequence that hybridizes with a polynucleotide sequence encoding SEQ ID NO:1-3, or 5.

Claim 22 is directed to a genus of proteins of any sequence that are encoded by a polynucleotide that hybridizes to the polynucleotide of SEQ ID NOs: 1-3 or 5. The Specification describes one example of a protein from Carybdea rastonii with hemolytic activity (SEQ ID NO:5). A search of the sequence database revealed that the structure (sequence) of the protein of the invention was unrelated to any other. Thus, the protein sequence appears to be unique.

For a claim drawn to a genus, the written description requirement for the claimed genus may be satisfied through sufficient description of a representative number of identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see Written Description Guidelines, p. 1106, Col. 3, paragraph 2-3).

In the present case, only one species has been described by actual reduction to practice. The single disclosed species in the present case is not sufficient to describe

the genus because the genus is highly variable. The claims encompass any amino acid sequence that gives hemolytic activity or any amino acid sequence encoded by a polynucleotide that hybridizes under any conditions (stringent or not) to the polynucleotides encoding SEQ ID NOs: 1-3 or 5. Since proteins that have hemolytic activity may vary in biochemical function and mechanism causing that hemolytic activity, it would be expected that proteins with hemolytic activity would be highly variable in sequence. Moreover, proteins that can have any function or sequence so long as the polynucleotide encoding them hybridizes to the polynucleotide encoding SEQ ID NO:5 or the short peptides of SEQ ID NO: 1-3 would be infinitely variable.

There are no common attributes that identify proteins as members of the genus. The Specification does not provide any identifying characteristics of hemolytic proteins from Carybdea rastonii so as to distinguish them from other hemolytic proteins. The specification is silent as to the specific biochemical function (the biochemical function that results in the hemolytic activity; e.g. binding or catalytic) of the claimed protein and the Specification does not provide guidance as to what effect changing any of the amino acids has on the function of the resulting phenotype. The general knowledge and level of skill in the art do not supplement the omitted description with respect to what amino acids are important. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:5 alone is insufficient to describe the genus. Thus, the claims are not supported by an adequate written description because a representative number of species have not been described.

The examiner notes that amending the claims to be directed to an isolated protein comprising the amino acid sequence of SEQ ID NO:5 or a composition comprising an isolated protein comprising the amino acid sequence of SEQ ID NO:5 would overcome this rejection.

Response to Arguments:

Applicants argue that the claim is limited to the gene library of C. rastonii and sequences according to SEQ ID NOs: 1-3 or 5. This argument has been considered but is not deemed persuasive for the following reasons. There are no common attributes that identify proteins as members of the genus. The Specification does not provide any identifying characteristics of hemolytic proteins from C. rastonii so as to distinguish them from other hemolytic proteins. The limitation that the claimed protein is produced by a polynucleotide that hybridizes with a polynucleotide "based on the amino acid sequence" of one of SEQ ID NOs: 1-3 or 5 does not further narrow the claimed genus. Almost any polynucleotide could hybridize to another given the appropriate conditions. Thus, the polynucleotide sequences that could hybridize to the polynucleotides "based on the amino acid sequence" of SEQ ID NOs: 1-3 or 5 are limitless. Moreover, the specification is silent as to the specific biochemical function (the biochemical function that results in the hemolytic activity; e.g. binding or catalytic) of the claimed protein and the Specification does not provide guidance as to what effect changing any of the amino acids has on the function of the resulting phenotype. The general knowledge and level of skill in the art do not supplement the omitted description with respect to what amino acids are important. Since the disclosure fails to describe the common attributes or

characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:5 alone is insufficient to describe the genus. Thus, the claims are not supported by an adequate written description because a representative number of species have not been described. Thus, the rejection is maintained.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 22 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 22, as amended, does not sufficiently distinguish over proteins as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught by page [insert page number] of specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is indefinite as to what is meant by a "based on an amino acid sequence". Does this mean that the polynucleotide sequence encodes the amino acid sequences claimed or can the polynucleotide be more distantly related to the amino acid sequence (e.g. the complement sequence to the sequence that encodes the claimed amino acid sequences or a nucleotide sequence that is only similar to one encoding the claimed amino acid sequence)? Clarification is required.

Conclusion

Claim 22 is rejected. Claim 17 appears to be in condition for allowance. A thorough search of the prior art did not reveal any teaching or suggestion of a protein having the sequence of SEQ ID NO:5.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 19-21, 23-31, and 33-35 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

HS

Holly Schnizer
December 4, 2002

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600